Remarks

Claims 1, 2, 6-11 and 22-24 are pending and have been rejected under 35 U.S.C. 101, 102(b), 102(e), 112(2nd), and 103. Without acquiescing in any rejection, applicants have replaced the pending claims with new claims 25 to 43 and provide arguments for the new claims. Claims 25 to 39 contain additional recitation "can bind human spermatozoa at least 10 times as strong as an equivalent molar amount of mouse ZP3" taken from page 14 lines 23-24 of the specification. Claims 40 to 41 contain the recitation "smaller than 10kd" and "can bind human spermatozoa with greater affinity than mouse spermatozoa." These recitations are supported by the specification throughout, for example, on page 7 lines 7-9, page 8, from 10 to 13 lines from the bottom, the last four lines on page 8, and page 9 lines 6-8. Claims 36, 37, 39 and 41 recite amino substitutions that are described in Table 1 and on page 10 lines 14-16. Recitation of ovarian cell lines in claim 35 is supported by the specification on page 18 lines 7-8. Recitation of protein size in claims 38 and 40 is supported by the specification, for example, on page 5 two lines from the bottom, page 6, 5 lines from the top. The term "10kd" is supported, for example, on page 14 line 14. Recitation of "that can stimulate the acrosome reaction of human spermatozoa when co-present with the spermatozoa at a concentration of less than 1 ug/ml for a time period of less than one hour" in claims 42 and 43 is supported by the specification on page 13, lines 6 to 10.

The language "predicted O-glycosylation site at a serine that corresponds to position 344 of the human ZP3 sequence five positions from the carboxyl terminus of the active portion of the human ZP3 sequence" in claim 27 is supported, for example, on page 10 lines 7-8 and page 9 lines 20-21 of the specification. Accordingly no new matter has been added to the claims.

The new claims have been written with specific language that clarifies the claims. Reconsideration and allowance are respectfully requested.

Priority

A claim to priority has been added as a first sentence to the specification, as requested by the Examiner on page 2 of the Office Action.

Information Disclosure Statement

An Information Disclosure Statement is submitted in response to the Examiner's request.

Oath/Declaration

A new declaration and oath are submitted in response to the Examiner's request.

Objection to the Specification

In response to this objection, the offending term "Id" has been replaced with a more specific reference.

Rejections Under 112 2nd Paragraph

Claims 1 and 22 are rejected because of the recitation "acrosome reaction." This term has been removed new claims 25 to 41, mooting the rejection. New claims 42 and 43 contain specific concentration and time parameters to clarify this term. Reconsideration and allowance are requested.

Claim 2, (now claim 26) was rejected for use of the term "produced." As suggested by the Examiner on page 5 of the Office Action, this term has been replaced with "expressed by." Reconsideration and allowance are requested.

Claim 6 has been rejected for reciting "binds to human sperm." The new claims now recite "can bind human spermatozoa at least 10 times as strong as an equivalent molar amount of mouse ZP3." This new language is very understandable and a skilled artisan knows how to routinely test such binding, as outlined, for example, on the bottom of page 14 in the specification.

Claim 6, (now 27) maintains the term "predicted." As described, for example on page 2 last seven lines in the specification, routinue methods exist for predicting whether an 0 glycosylation will occur at a site. Further, while wishing not to be bound by any one theory of their invention because it is not needed to make and use the invention, applicants have identified that a particular region, residues 308 to 348, and a particular serine residue at position 344 plays a major role in the biological species specific effect discovered by glycosylation of one representative human ZP3 sequence by human ovary cells. See, for example, page 9 middle and last paragraphs from the specification. Applicants stress that related terms such as "likely glycosylated" (11 lines from bottom) and "drastically less predicted glycosylation" refer to the probability that a glycosidic enzyme will glycosylate a given site on a given molecule and that such mass properties readily are ascertained by measuring a large number of molecules in an assay. That is, glycosylation in reality is probability based, depending on the amino acid environment around the residues that are recognized by glycosidic enzymes, particularly for those enzymes that O-glycosylate serines and theonines. The "prediction" of glycosylation of position 344 of a human-like sequence, in particular is based on solid science, as pointed out in the first full paragraph on page 10.

Applicants further point out that the type of binding referred to does not require a large intact protein structure, such as from an antibody or antibody fragment. Accordingly, conservative amino acid substitutions, as detailed on page 10, middle can be made and work in the claimed invention. The effects of and reliability of these substitutions are much greater than that of substituting conservative amino acids in enzymes

and antibodies. Applicants submit that the decision in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. Int. 1989) is applicable here. In *Mark*, appellant Mark presented claims to a mutein of a "biologically active protein" where at least one cysteine residue that was "non-essential to said biological activity" was "substituted by another amino acid." In reversing the examiner on enablement grounds, the Board reasoned that:

To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [the] declaration to be persuasive that only routine experiementation would be needed for one skilled in the art to practice the invention for a given protein. The fact that a given protein might not be amenable for use in the present invention in that the cysteine residues are needed for biological activity does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity. *Ex parte Mark*, 12 USPQ2d at 1907.

In fact, the claims in *Mark* were quite broad because they pertained to **any** protein with **any** type of biological activity. Thus, the claims in *Mark*, which were considered enabled by the Board, required the skilled artisan to determine which cysteine residues could be removed ***in any given*** protein without adversely impacting the three-dimensional structure of the protein. In contrast, applicants' claims 36-38 and 41 are directed to a range of amino acids that provide suitable glycosylation, and the claimed sequences do not even have to have the same antigenic epitopes. That is, based on peer-reviewed information the amino acid substitutions provide suitable sites for glycosylation.

It also is important to note that the *Mark* decision issued in 1989 for an application that was filed even earlier. Applicants' first filed application was filed in 1998, almost ten years after the *Mark* decision. Suffice it to say, technology has advanced over the years, which inures to the benefit of applicants' enablement. Applicants therefore request withdrawal of the rejection.

Claims 23 and 24 are rejected over the use of the term "hZP3" and "PA-1." The new claims do not recite "hZP3," mooting the former rejection. PA-1 is described as an ovarian cell line on page 9 line 6 of the specification and by the language of new claim 35. Reconsideration and allowance are earnestly requested.

Rejection Under 35 U.S.C. 101

Claims that recite an entire ZP3 protein now recite "purified" as suggested by the Examiner on page 7 of the Office Action. Claims 38-40 concern smaller polypeptides that are not found in nature. Reconsideration and allowance are requested.

Rejection Under 35 U.S.C. 102(b),(e)

On page 7 (item 12) the Examiner has rejected claims 1,2, 6-11 and 22 on anticipation grounds over Van Duin (WO 92/03548), arguing that "Van Duin disclosed a polypeptide and functional derivatives thereof which have human ZP3 activity or human ZP3 antigenicity."

In response, applicants point out that the claimed invention is not to a molecule that cross-reacts with human ZP3 but instead, to a glycoprotein that is fully functional in terms of human ZP3 activity. A major point of the inventors' work is that earlier attempts to clone human ZP3 did not produce the inventive material. New claims 25-41 are distinguished from such prior art, among other reasons, by the element "that can bind human spermatozoa at least 10 times as strong as an equivalent molar amount of mouse ZP3" to denote this difference. All previously synthesized ZP3 lacked this claim capability. New claims 42 and 43 are distinguished from prior art by the element that the ZP3 "can stimulate the acrosome reaction of human spermatozoa when co-present with the spermatozoa at a concentration of less than 1 ug/ml for a time period of less than one hour." The applicants found, as described in the examples, that ZP3 according to the claimed invention differs from other rZP3 by the ability to stimulate the acrosome reaction at this range of concentrations for this time period.

Because the new claims recite an element that is lacking in the cited document, the Examiner respectfully is requested to withdraw this rejection.

On page 8 (II) the Examiner has rejected claims 1,2, 6-11 and 22 on anticipation grounds over Harris et al. (WO 94/11019). This anticipation argument arises from the

observation that Harris teaches methods useful for the recombinant production of ZP3. However Harris has not made the product that is subject to these claims. The Examiner points out that Harris discusses mouse ZP3 and human ZP2 (ZPA and ZPB). However the scope of the new claims does not extend to mouse ZP3 or to human ZP2.

Because the new claims recite protein that is not included in Harris, the Examiner respectfully is requested to remove this rejection.

On page 9 (III) the Examiner has rejected claims 1,2, 6-11 and 22 on anticipation grounds, arguing that Harris U.S. No. 5,837,497 anticipates these claims. Applicants point out in response that the scope of the claims does not include porcine recombinant ZP3, monkey recombinant ZP3, canine recombinant ZP3, human ZP3 DNA, or chemically synthesized human ZP3 peptides. The claims are to human ZP3 glycoprotein having glycosylation characteristic of human ovarian cells that provides specific binding, as compared with mouse ZP3. Harris did not prepare such glycoprotein.

Because the new claims recite protein that is not included in Harris, the Examiner respectfully is requested to remove this rejection.

Rejections Under 35 U.S.C. 103

On pages 10-12 the Examiner has rejected claims 23 and 24 (which recite human ZP3 prepared from the PA-1 cell line) on obviousness grounds in view of five references.

No Prima Facie Case

For an obviousness rejection, each claim element must be specifically recited somewhere in the references and inherency cannot be relied on. A glycopolypeptide "that can bind human spermatozoa at least 10 times as strong as an equivalent molar amount of mouse ZP3" is not provided in any of the references. None of the cited documents suggest or state this claim element. Any speculation about a ZP3 that might be made and have the suitable carbohydrate or have this as an inherent feature does not suffice for a prima facie case.

Accordingly, a prima facie case of obviousness has not been established and the Examiner respectfully is requested to withdraw this rejection.

The Cited References are Not Relevant or Teach Away

The Examiner points out (page 11, bottom, to page 12) that the references teach generation of purified DNA coding for human ZP3. However, a search of the Stern et al. (US 5,869,053) patent fails to reveal even a single mention of ZP3. Further, Stern has only a single mention of PA-1 within a long table of about 35 other cell types and does not even use any word such as glycoprotein, glycopeptide, glycosidase or the like anywhere within the text (outside of cited references). This lone mention of PA-1 teaches, if anything, that the surface of PA-1 cells may relate to an antibody that binds to the cells. This does not even teach use of PA-1 cell line as a vehicle to make a protein. This reference does not support any kind of combination of a PA-1 cell with ZP3 expression or even a thought about any role of a carbohydrate in any kind of biological or biochemical process. Moreover, this patent is all about immunoreactivity, which is unrelated and actually opposite to the invention.

Assuming for the sake of argument that a reader actually tried to learn the invention (even in hindsight) by reading Stern, the reader would learn that amino acid sequence is important in binding, and would be led away from the claimed invention. Stern teaches that the amino acid sequence of an expressed protein is used for reactivity for binding to antibody and that antibodies can bind to cell surfaces. This particularly teaches away from the invention. The mere fact that PA-1 is mentioned once within a long list of cell types seems unrelated to any kind of combination that might relate to the invention, particularly since Stern studied antibody binding activity to protein. Thus, the references teach away from combining the remaining elements.

The Applicants submit that the present invention is now in condition for allowance.

Early notification of such action is courteously solicited.

Respectfully submitted,

June 28, 2000
Date

Marvin Motsenbocker
Registration No. 36,614

FOLEY & LARDNER
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5109
Telephone: (202) 672-5300
Facsimile: (202) 672-5399

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